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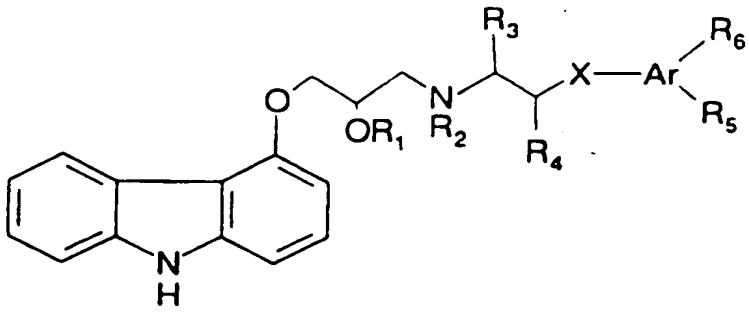
(54) Title: USE OF CARBAZOLE COMPOUNDS FOR THE TREATMENT OF CONGESTIVE HEART FAILURE

(57) Abstract

A method of treatment using a compound of formula (I), wherein R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl; R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl; R_3 is hydrogen or lower alkyl of up to 6 carbon atoms; R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$; X is a valency bond, $-CH_2$, oxygen or sulfur; Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl; R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphonyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or R_5 and R_6 together represent methylenedioxy; or a pharmaceutically acceptable salt thereof, preferably carvedilol, alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of ACE inhibitors, diuretics, and cardiac glycosides for decreasing mortality resulting from congestive heart failure (CHF) in mammals, particularly humans.



(I)

USE OF CARBAZOLE COMPOUNDS FOR THE TREATMENT OF CONGESTIVE HEART FAILURE

Field of the Invention

The present invention relates to a new method of treatment using compounds which are dual non-selective ß-adrenoceptor and α_1-adrenoceptor antagonists, in particular the carbazolyl-(4)-oxypropanolamine compounds of Formula I, preferably carvedilol, for decreasing the mortality of patients suffering from congestive heart failure (CHF). The invention also relates to a method of treatment using compounds which are dual non-selective ß-adrenoceptor and α_1-adrenoceptor antagonists, in particular the carbazolyl-(4)-oxypropanolamine compounds of Formula I, preferably carvedilol, in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of angiotensin converting enzyme (ACE) inhibitors, diuretics, and cardiac glycosides, for decreasing the mortality of patients suffering from CHF. The invention further relates to an incremental application scheme for administering compounds which are β-adrenoreceptor and α_1-adrenoreceptor antagonists.

Background of the Invention

Congestive heart failure occurs as a result of impaired pumping capability of the heart and is associated with abnormal retention of water and sodium. Traditionally, treatment of chronic mild failure has included limitation of physical activity, restriction of salt intake, and the use of a diuretic. If these measures are not suffcient, a cardiac glycoside, which is an agent that increases the force of mycardial contraction, is typically added to the treatment regimen.

Subsequently, angiotensin converting enzyme inhibitors, which are compounds that prevent the conversion of angiotensin I into the pressor-active angiotensin II, are prescribed for chronic treatment of congestive heart failure, in conjunction with a diuretic, a cardiac glycoside, or both.

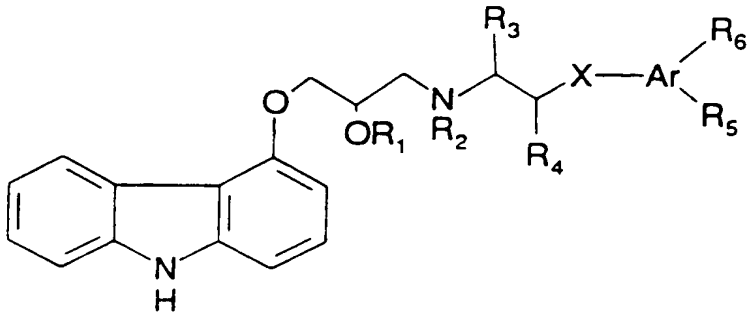
Also, congestive heart failure is a well-known cardiac disorder which results in an excess mortality. Applefeld, M.M., (1986) Am. J. Med., 80, Suppl. 2B, 73-77. Therefore, therapeutic agents that would decrease the mortality resulting from CHF in patients suffering therefrom are highly desirable.

Summary of the Invention

The present invention provides a new use of compounds which are dual non-selective ß-adrenoceptor and α_1-adrenoceptor antagonists for the preparation of medicaments for the treatment of congestive heart failure. In particular, the carbazolyl-(4)-oxypropanolamine compounds of Formula I are preferred, alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of ACE inhibitors, diuretics, and cardiac glycosides, as therapeutics for decreasing mortality resulting from congestive heart failure in mammals, particular. In particular, the present invention preferably provides a method of treatment, alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of ACE inhibitors, diuretics, and cardiac glycosides, for the compound of Formula I wherein R_1 is -H, R_2 is -H, R_3 is -H, R_4 is -H, X is 0, Ar is phenyl, R_5 is ortho -OCH_3, and R_6 is -H, said compound being better known as carvedilol, which is (1-(carbazol-4-yloxy-3-[[2-(2-methoxyphenoxy) ethyl]amino]2-propanol), or a pharmaceutically acceptable salt thereof.

Detailed Description of the Invention

U.S. Pat. No. 4,503,067 discloses carbazolyl-(4)-oxypropanolamine compounds of Formula I:



(I)

wherein

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$;

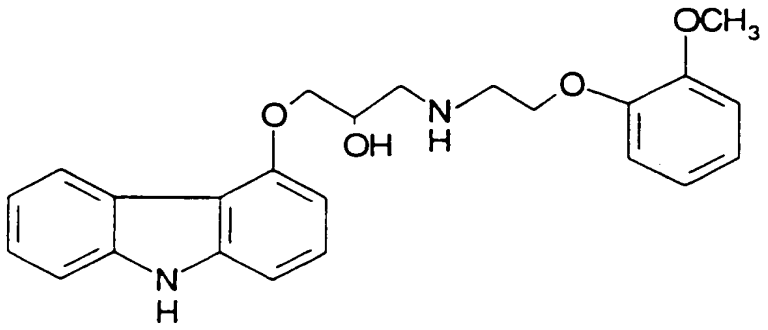
X is a valency bond, $-CH_2$, oxygen or sulfur;

Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -$CONH_2$- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphonyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy; and pharmaceutically acceptable salts thereof.

This patent further discloses a compound of Formula I, better known as carvedilol, which is (1-(carbazol-4-yloxy-3-[[2-(2-methoxyphenoxy)ethyl]amino](2-propanol), having the structure shown in Formula II:



(II)

Formula I compounds, of which carvedilol is exemplary, are novel multiple action drugs useful in the treatment of mild to moderate hypertension. Carvedilol is known to be both a competitive non-selective ß-adrenoceptor antagonist and a vasodilator, and is also a calcium channel antagonist at higher concentrations. The vasodilatory actions of carvedilol result primarily from α_1-adrenoceptor blockade, whereas the ß-adrenoceptor blocking activity of the drug prevents reflex tachycardia when used in the treatment of hypertension. These multiple actions of carvedilol are responsible for the antihypertensive efficacy of the drug in animals, particularly in humans. See Willette, R.N., Sauermelch, C.F. & Ruffolo, R.R., Jr. (1990) Eur. J. Pharmacol., 176, 237-240; Nichols, A.J., Gellai, M. & Ruffolo, R.R., Jr. (1991) Fundam. Clin. Pharmacol., 5, 25-38; Ruffolo,

R.R., Ir., Gellai, M., Hieble, J.P., Willette, R.N. & Nichols, A.J. (1990) Eur. J. Clin. Pharmacol., 38, S82-588; Ruffolo, R.R., Ir., Boyle, D.A., Venuti, R.P. & Lukas, M.A. (1991) Drugs of Today, 27, 465-492; and Yue, T.-L., Cheng, H., Lysko, P.G., Mckenna, P.J., Feuerstein, R., Gu, I., Lysko, K.A., Davis, L.L. & Feuerstein, G. (1992) J. Pharmacol. Exp. Ther., 263, 92-98.

The antihypertensive action of carvedilol is mediated primarily by decreasing total peripheral vascular resistance without causing the concomitant reflex changes in heart rate commonly associated with other antihypertensive agents. Willette, R.N., et al. supra; Nichols, A.J., et al. supra; Ruffolo, R.R., Jr., Gellai, M., Hieble, J.P., Willette, R.N. & Nichols, A.1. (1990) Eur. J. Clin. Pharmacol., 38, S82-S88. Carvedilol also markedly reduces infarct size in rat, canine and porcine models of acute myocardial infarction, Ruffolo, R.R., Jr., et al., Drugs of Today, supra, possibly as a consequence of its antioxidant action in attenuating oxygen free radical-initiated lipid peroxidation. Yue, T.-L., et al. supra.

Recently, it has been discovered in clinical studies that pharmaceutical compounds which are dual non-selective ß-adrenoceptor and α_1-adrenoceptor antagonists, in particular the compounds of Formula I, preferably carvedilol, alone or in conjunction with conventional agents, said agents being ACE inhibitors, diuretics, and cardiac glycosides, are effective therapeutic agents for treating CHF. The use of agents, such as carvedilol in treating CHF is surprising, since, in general, ß-blockers are contraindicated in patients suffering from heart failure, because ß-blockers are known to have undesirable cardiodepressive effects. The most surprising observation from the studies in which the instant compounds were used to treat CHF is that said compounds, in particular carvedilol, are able to decrease the mortality resulting from CHF in humans by about 67 percent. Furthermore, this result is present across all classifications of CHF and both etiologies (eschemic and non-eschemic). This result is surprising since two recent mortaiity studies using the ß-blockers metoprolol (Waagstein, et al., (1993) Lancet, 342, 1441-1446) and bisoprolol (CIBIS investigators and committees, (1994) Circulation, 90, 1765-1773) in the

treatment of CHF showed no difference in mortality between drug-treated patients and placebo-treated patients.

According to the method of treatment of the present invention, the desirable therapeutic effect of the compounds of Formula I, particularly carvedilol, may be augmented by using any one of said compounds; or any pharmaceutically acceptable salt of said compounds, in conjunction with ACE inhibitors, diuretics, and cardiac glycosides, which are effective therapeutic agents for the treatment of CHF. In particular, the preferred ACE inhibitors of the present invention are selected from the group consisting of captopril, lisinopril, fosinopril and enalapril, or any pharmaceutically acceptable salts thereof and the preferred diuretics of the present invention are hydrochlorothiazide furosemide, or torasemide or any pharmaceutically acceptable salts thereof. The preferred cardiac glycosides of the present invention are digoxin, β-methyldigoxin or digitoxin. The desireable therapeutic benefits of the compounds of Formula I, particularly carvedilol, are additive with those of such ACE inhibitors, or diuretics, or cardiac glycosides when administered in combination therewith. Captopril is commercially available from E.R. Squibb & Sons, Inc. Lisinopril, enalapril and hydrochlorothiazide are commercially available from Merck & Co. Furosemide is commercially available from Hoechst-Roussel Pharmaceuticals, Inc. Digoxin is commercially available from Burroughs Wellcome Co. and Boehringer Mannheim GmbH. Digitoxin, β-Methyldigoxin, fosinopril and torasemide are commercially available from Boehringer Mannheim GmbH.

Compounds of Formula I may be conveniently prepared as described in U.S. Pat. No. 4,503,067. Carvedilol is commercially available from SmithKline Beecham Corporation and Boehringer Mannheim GmbH (Germany).

Pharmaceutical compositions of the compounds of Formula I, including carvedilol, alone or in combination with ACE inhibitors, or diuretics, or cardiac glycosides may be administered to patients according to the present invention in any medically acceptable manner, preferably orally. For parenteral administration, the pharmaceutical composition will be in the form of a sterile injectable liquid stored in a suitable container such as an

ampoule, or in the form of an aqueous or nonaqueous liquid suspension. The nature and composition of the pharmaceutical carrier, diluent or excipient will, of course, depend on the intended route of administration, for example whether by intravenous or intramuscular injection.

Pharmaceutical compositions of the compounds of Formula I for use according to the present invention may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as ethanol, polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternatively, these compounds may be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, ethanol, and water. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension.

Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

Compounds having the above-mentioned dual properties are preferably administered following a three-stage application scheme. This scheme is characterized by the fact that incremental dosages of the active ingredient are administered to patients over a certain period of time, until the regular maintenance dosage is received. If this maintenance dosage is defined as the setting value being 100 %, it was found that the application regimen in a first phase should extend for a period of 7 - 28 days, whereby only 10-30 % of the setting dose are administered. Following this phase, a second application regimen should follow, wherein a dosage of 20 - 70 % of the setting dose is administered to the patient for a period of 7 - 28 days. After termination of this phase, the third application period follows, wherein the daily complete setting dose (maintenance dose) is administered. The daily maintenance dose can vary between 10 - 100 mg of said active ingredient.

In case of carvedilol, dosing in humans for the treatment of disease according to the present invention should not exceed a dosage range of from about 3.125 to about 50 mg of the compounds of Formula I, particularly carvedilol, preferably given twice daily. As one of ordinary skill in the art will readily comprehend, the patient should be started on a low dosage regimen of the desired compound of Formula I, particularly carvedilol, and monitered for well-known symptoms of intolerance, e.g., fainting, to such compound. Once the patient is found to tolerate such compound, the patient should be brought slowly and incrementally up to the rnaintenance dose. The preferred course of treatment is to start the patient on a dosage regimen with formulations which contain either 3.125 or 6.25 mg of active compound per single unit, preferably given twice daily, for 7 - 28. days. The choice of initial dosage most appropriate for the particular patient is determined by the practitioner using well-known medical principles, including, but not limited to, body weight. In the event that the patient exhibits medically acceptable tolerance of the compound for two weeks, the dosage is doubled at the end of the two weeks and the patient is maintained at the new, higher dosage for an additional period,

preferably to two more weeks, and observed for signs of intolerance. This course is continued until the patient is brought to a maintenance dose. The preferred maintenance dose is 25.0 mg of active compound per single unit, preferably given twice daily, for patients having a body weight of up to 85 kg. For patients having a body weight of over 85 kg, the maintenance dose is between about 25.0 mg and about 50.0 mg, preferably given twice daily; preferably about 50.0 mg of active compound per single unit, preferably given twice daily.

The present invention relates also to method of treatment for decreasing mortality resulting from congestive heart failure in mammals comprising internally administering to said mammal in need thereof an effective amount of carvedilol according to the following schedule:

(a) a pharmaceutical formulation which contains either 3.125 or 6.25 mg carvedilol per single unit for a period of 7 - 28 days, given once or twice daily,

(b) thereafter a pharmaceutical formulation which contains 12.5 mg carvedilol per single unit for a period of additional 7 - 28 days, given once or twice daily, and

(c) finally a pharmaceutical formulation which contains either 25.0 or 50.0 mg carvedilol per single unit, given once or twice daily as a maintenance dose.

Dosing in humans for the treatment of disease according to the present invention includes the combination of compounds of Formula I with conventional agents. For example, the usual adult dosage of hydrochlorothiazide is 25 - 100 mg daily as a single dose or divided dose. The recommended starting dose for enalapril is 2.5 mg administered once or twice daily. The usual therapeutic dosing range for enalapril is 5 - 20 mg daily, given as a single dose or two divided doses. For most patients the usual initial daily dosage of captopril is 25 mg three times per day (tid), with most patients having a satisfactory clinical improvement at 50 or 100 mg three times per day (tid).

It will be appreciated that the actual preferred dosages of the compounds being used in the compositions of this invention will vary according to the particular composition formulated, the mode of administration, the particular site of administration and the host being treated.

No unacceptable toxicological effects are expected when the compounds of Formula I, including the compound of Formula II, are used according to the present invention. The example which follows is intended in no way to limit the scope of this invention, but is provided to illustrate how to use the compounds of this invention. Many other embodiments will be readily apparent to those skilled in the art.

Experimental

Mortality Studies in CHF Patients

Summary. To determine if ß-adrenergic blockade might inhibit the deleterious effects of the sympathetic nervous system on survival in heart failure (CHF), 1052 patients with CHF were prospectively enrolled into a multicenter trial program, in which patients were randomly assigned (double-blind) to 6-12 months' treatment with placebo (PBO) or carvedilol (CRV),. After a common screening period, patients with class II-IV CHF (see next paragraph for the definitions of the classification of CI) and an ejection fraction < 0.35 were assigned to one of four protocols based on performance on a 6-minute walk test. PBO or CRV was added to existing therapy with digoxin, diuretics and an ACE inhibitor. All-cause mortality was monitored by a prospectively constituted Data and Safety Monitoring Board (DSMB). After 25 months of enrollment, the DSMB recommended termination of the program because of a favorable effect of CRV on survival. By intention-to-eat, mortality was 8.2% in the PBO group but only 2.9% in the CRV group (P = 0.0001, Cochran-Mantel-Haensel analysis). This represented a reduction in risk of death by CRV of 67% (95% CI: 42% to 81 %). The treatment effect

was similar in patients with class II and class III-IV symptoms. Mortality was -educed in class II patients from 5.9% to 1.9%, a 68% reduction (95% CI: 20% to 97%) [P = 0.015,), and in class III-IV patients from 11.0% to 4.2%, a 67% reduction (95% CI: 30% to 84%), [P = 0.004, log-rank]. Importantly, the effect of CRV was similar in ischemic heart disease (risk reduced by 67%, P = 0.003) and in nonischemic dilated cardiomyopathy (risk reduced by 67%, P = 0.014). In conclusion, the addition of CRV to conventional therapy is associated with a substantial (67%) reduction in the mortality of patients with chronic CHF. The treatment effect is seen across a broad range of severity and etiology of disease.

As used herein, by "Class II CHF" is meant patients with cardiac disease resulting in slight or moderate limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain. By "Class III CHF" is meant patients with cardiac disease resulting in marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain. By "Class IV CI" is meant patients with cardiac disease resulting in inability to car on any physical activity without discomfort, symptoms or cardiac insufficiency, or of the anginal syndrome. By "less than ordinary physical activity" is meant climbing one flight of stairs, or walking two hundred yards.

Design of Study. Patients on background therapy with diuretics, ACE inhibitors and/or digoxin were stratified on the basis of baseline submaximal exercise performance, into one of four trials:

- study 220, a dose response study in moderate (NYHA II-IV) CHF with exercise testing as a primary endpoint

- study 221, a dose titration study in moderate (NYHA II-IV) CI with exercise testing as a primary endpoint

- study 239. a dose titration study in severe (NYHA III-IV) CHF with quality of life as a primary endpoint

- study 240. a dose titration study in mild (NYHA II-III) CHF with progression of CHF as a primary endpoint

Sixty-four centers in the US participated in the trial program. All sites conducted protocols 239 and 240, while 33 performed protocol 220 and 31 performed protocol 221.

Although each trial had its own individual objectives, the overall program objective defined prospectively was evaluation of all-cause mortality. Based upon a projected enrollment of 1100 patients, the program had 90% power to detect a 50% reduction in mortality (two-sided) between carvedilol and placebo, assuming a mortality rate in the placebo group of 12% over the duration of the trials $\alpha = 0.05$).

Randomization was preceded by a screening and challenge period common to the four protocols The purpose of the screening period was to qualify patients for study entry, obtain reproducible baseline measurements, and stratify patients into the appropriate trial based on submaximal exercise testing. During the challenge period, patients received low-dose open-label carvedilol (6.25 mg b.i.d.) for two weeks. Patients unable to tolerate this dose did not proceed to randomization. Patients tolerating low-dose carvedilol were then randomized to blinded medication (carvedilol or placebo) with the dose titrated over several weeks in the range of 6.25 to 50 mg b.i.d. (or equivalent level of placebo). The maintenance phase of each study ranged from six to 12 months, after which patients had the option of receiving open-label carvedilol in an extension study.

Results. The analysis presented below corresponds to the data set on which the DSMB made the recommendation to terminate the trials. Included in this intent-to-eat analysis are all patients enrolled in the US trials as of January 20, 1995; 624 receiving carvedilol

and 356 placebo. An analysis of baseline patient characteristics (Table 1) shows good balance between the randomized groups.

Table 1: US Carvedilol Heart Failure Trials - Baseline Characteristics

Characteristic	Placebo (n = 356)	Carvedilol (n = 624)
Age, mean + SD (years)	59.9+11.7	58.8+11.8
Sex (% men)	62%	62%
Etiology (% ischemic)	43%	40%
Severity of CHF		
Class II	41%	41%
Class III-IV	40%	39%
Unknown	19%	20%
LV ejection fraction, mean + SD	0.22 + 0.07	0.23 + 0.08
6 Minute walk (m + SD)	373+88	379+81
Blood pressure (mmHg)	115/73	115/73
Heart rate (bpm + SD)	85 ± 13	86 ± 13

The overall mortality results for the program are shown in Table 2. All deaths that occurred during the intent-to-treat period are included. Treatment with carvedilol resulted in a 67% reduction in the risk of all-cause morality. Analysis of mortality by certain baseline characteristics shows this to be a broad effect regardless of severity or etiology of CI. The effect was uniform in patients with mild heart failure or moderate to severe heart failure. Similarly, the mortality reduction was equivalent in patients with ischemic or non-ischemic heart failure.

Table 2: Evaluation of Mortality in US Carvedilol CHF Studies

	Carvedilol	Placebo	Risk reduction (95 % CI)	p value*
All Cause Mortality	18/624 (2.9 %)	29/356 (8.2 %)	67 % (42 - 81)	< 0.001
Class II CHF	7/361 (1.9 %)	12/202 (5.9 %)	68 % (20 - 97)	0.015
Class III-IV CHF	11/263 (4.2 %)	17/154 (11.0 %)	66 % (30 - 84)	0.004
Ischemic Etiology	10/311 (3.2 %)	16/178 (8.9 %)	67 % (32 -85)	0.003
Non-Ischemic Etiology	8/313 (2.5 %)	13/178 (7.3 %)	67 % (20 - 86)	0.014

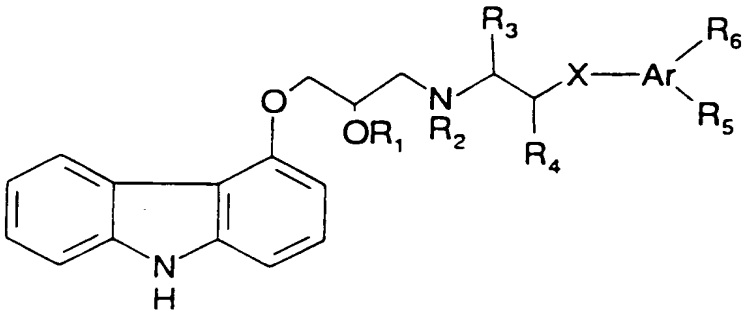
*Cochran-Mantel-Haensel Anatysis

The foregoing is illustrative of the use of the compounds of this invention. This invention, however, is not limited to the precise embodiment described herein, but encompasses all modifications within the scope of the claims which follow.

Claims

1. The use of a compound which is both a β-adrenoreceptor antagonist and a α_1-adrenoreceptor antagonists for the manufacture of a medicament for decreasing mortality resulting from congestive heart failure in mammals, alone or in conjunction with one or more other therapeutic agents, said agents selected from the group consisting of an angiotensin converting enzyme inhibitor, a diuretic and a cardiac glycosides.

2. The use of a compound according to claim 1, wherein said compound is subject of formula I



(I)

wherein

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$;

X is a valency bond, $-CH_2$, oxygen or sulfur;

Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphonyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy; and pharmaceutically acceptable salts thereof.

3. The use of a compound according to claim 1 or 2, wherein said compound is carvedilol.

4. The use of a compound according to claim 3, whereby a pharmaceutical formulation containing either 3.125 or 6.25 mg carvedilol in a single unit are administered for a period of 7 - 28 days, once or twice daily as an initial dose.

5. The use of a compound according to claim 3, whereby a pharmaceutical formulation containing 12.5 mg carvedilol in a single unit are administered for a period of 7 - 28 days, once or twice daily.

6. The use of a compound according to claim 3, whereby a pharmaceutical formulation containing either 25.0 or 50.0 mg carvedilol in a single unit are administered once or twice as a maintenance dose.

7. The use of a compound according to claim 1, wherein said ACE inhibitor is selected from the group consisting of captopril, lisinopril, fosinopril or enalapril, or any pharmaceutically acceptable salt thereof.

8. The use of a compound according to claim 1, wherein said diuretic is selected from the group consisting of hydrochlorothiazide, torasemide or furosemide, or any pharmaceutically acceptable salt thereof.

9. The use of a compound according to claim 1, wherein said cardiac glycoside is selected from the group consisting of digoxin, β-methyl-digoxin or digitoxin.

10. The use of carvedilol for the manufacture of a medicament for decreasing mortality resulting from congestive heart failure in mammals according to the following regimen:

(a) administering a pharmaceutical formulation which contains either 3.125 or 6.25 mg carvedilol per single unit for a period of 7 - 28 days, given once or twice daily,

(b) administering thereafter a pharmaceutical formulation which contains 12.5 mg carvedilol per single unit for a period of additional 7 - 28 days, given once or twice daily and

(c) administering finally a pharmaceutical formulation which contains either 25.0 or 50.0 mg carvedilol per single unit, given once or twice daily as a maintenance dose.

11. The use of carvedilol according to claim 10, whereby carvedilol is administered in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of an angiotensin converting enzyme inhibitor, a diuretic and a cardiac glycoside.

12. Use of a compound according to claim 1 for the preparation of a medicament for the treatment of CHF to be administered in a daily maintenance dose of 10 - 100 mg, said medicament being administered in incremental dosage schems comprising three dose regimens, the first regimen comprising administering an amount of 10 - 30 % of the daily maintenance dose of the compound for a period of 7 - 28 days, the second regimen comprising administering an amount of 20 - 70 % of said daily dose for a period of 7 - 28 days and a third regimen comprising administering 100 % of said daily dose starting after termination of the second regimen.

13. Oral pharmaceutical formulation comprising an effective amount of 1.0 - 10.0 mg Carvedilol per single dose unit form.

14. Formulation according to claim 13 containing 2.5 - 7.5 mg Carvedilol.

11. The use of carvedilol according to claim 10. whereby carvedilol is administered in conjunction with one or more other therapeutic agents. said agents being selected from the group consisting of an angiotensin converting enzyme inhibitor. a diuretic and a cardiac glycoside.

12. Use of a compound according to claim 1 for the preparation of a medicament for the treatment of CHF to be administered in a daily maintenance dose of 10 - 100 mg, said medicament being administered in incremental dosage schems comprising three dose regimens. the first regimen comprising administering an amount of 10 - 30 % of the daily maintenance dose of the compound for a period of 7 - 28 days. the second regimen comprising administering an amount of 20 - 70 % of said daily dose for a period of 7 - 28 days and a third regimen comprising administering 100 % of said daily dose starting after termination of the second regimen.

13. Oral pharmaceutical formulation comprising an effective amount of 1.0 - 10.0 mg Carvedilol per single dose unit form.

14. Formulation according to claim 13 containing 2.5 - 7.5 mg Carvedilol.

14. Okt. 19

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A3

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(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

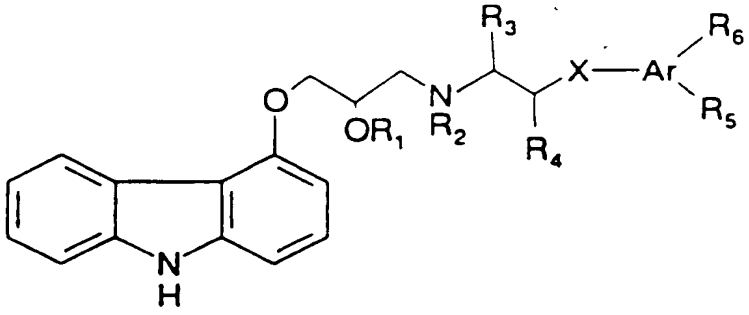
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report: 3 October 1996 (03.10.96)

(54) Title: USE OF CARBAZOLE COMPOUNDS FOR THE TREATMENT OF CONGESTIVE HEART FAILURE

(57) Abstract

A method of treatment using a compound of formula (I), wherein R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl; R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl; R_3 is hydrogen or lower alkyl of up to 6 carbon atoms; R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$; X is a valency bond, $-CH_2$, oxygen or sulfur; Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl; R_5 and R_6



(I)

are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphonyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or R_5 and R_6 together represent methylenedioxy; or a pharmaceutically acceptable salt thereof, preferably carvedilol, alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of ACE inhibitors, diuretics, and cardiac glycosides for decreasing mortality resulting from congestive heart failure (CHF) in mammals, particularly humans.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 15 August 1996 (15.08.96)	
International application No.: PCT/EP96/00498	Applicant's or agent's file reference: 4155/OA/WO-Wb
International filing date: 07 February 1996 (07.02.96)	Priority date: 08 February 1995 (08.02.95)
Applicant: LUKAS-LASKEY, Mary, Ann et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

18 July 1996 (18.07.96)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 730.91.11

T. 8.8.97

cc. Prof. Sponer
SB

T. 8.8.97

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
Weber, Manfred
BOEHRINGER MANNHEIM GMBH
Patentabteilung
D-68298 Mannheim
ALLEMAGNE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	06. 05. 97
Applicant's or agent's file reference: 4155/OA/WOWb	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 96/00498	07/02/1996	08/02/1995

Applicant

BOEHRINGER MANNHEIM PHARMACEUTICALS CORP. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	J. Lausenmeyer Telephone No.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4155/OA/WOWb		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 96/ 00498	07/02/1996	08/02/1995
International Patent Classification (IPC) or national classification and IPC		
A61K31/40		
Applicant		
BOEHRINGER MANNHEIM PHARMACEUTICALS CORP. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of 1 sheet.

3. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/07/1996	06.05.97
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	I. Obrecht Telephone No. 8471

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.
PCT/EP96/00498

I. Basis of the report

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

[ ] the international application as originally filed.

[x] the description, pages 1 - 14, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____,

[x] the claims, Nos. 1 - 10, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 11, 12, filed with the letter of 17.03.97,
Nos. _____, filed with the letter of _____,

[ ] the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:
[ ] the description, pages _____.
[ ] the claims, Nos. _____.
[ ] the drawings, sheets/fig _____.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1 - 12	YES
	Claims	NO
Inventive Step (IS)	Claims 1 - 12	YES
	Claims	NO
Industrial Applicability (IA)	Claims 1 - 12	YES
	Claims	NO

2. CITATIONS AND EXPLANATIONS

Some general remarks have been brought up to the attention of the International Preliminary Examining Authority:

Congestive heart failure (CHF) is a disease which is characterized by impaired function of the heart with the consequence that distinct organs are lacking of sufficient blood supply. CHF is not only a disease which markedly disables the patients, but life expectancy is highly decreased. For example, only 50% of CHF patients with a late state (NYHA IV) survive about 1 year, in mild forms (NYHA II-III) only 50% of the patients survive about 5 years. Therefore, in principle, goal of any treatment of CHF patients should be targeted to improve the symptoms (e.g. exercise capacity) and to reduce mortality.

For the treatment of CHF, digitalis glycosides, (loop-) diuretics and vasodilators have been used over decades. Digitalis glycosides increase the myocardial

contractility, improve hemodynamic variables and improve symptoms, but digitalis glycosides do not increase life expectancy as confirmed recently in the large epidemiological DIG-trial on about 7800 patients. Diuretics offload the heart by reducing the circulating blood volume and therefore, symptoms, in particular congestions, can be reduced by diuretics. There is no study available which shows that diuretics are able to reduce the mortality of CHF patients. This topic has never been studied. Also vasodilators can reduce the myocardial pre- and afterload and therefore, they can improve the symptoms. Among the different vasodilators, there are inconsistent data available with respect to reduction in mortality. Whereas α_1-adrenoreceptor have not been shown to reduce mortality, the combination of hydralazine + isosorbid dinitrate have been shown to improve the life expectancy to a very small extend (Cohn et Al 1986). Phosphodiesterase inhibitors (e.g. milrinone) induce very nice hemodynamic effects and improve exercise capacity, but they induces excess mortality (Di Bianco et al. 1989).

On the other hand, in a variety of studies, ACE inhibitors have consistently demonstrated to be effective not only in improving the symptoms but also in a prolongation of life expectancy. In summary, there is no correlation between improvement of hemodynamic variables or relief of symptoms and reduction in mortality of patients treated with various drugs. Thus, the goal, to treat the patients for feeling better and living longer was an wish not met in the past due to the fact that life expectancy could mostly not be improved by the compounds.

With respect to ß-blockers:

In general, ß-blockers are contra-indicated for patients in CHF due to their negative inotropic effect. However, some studies have been performed in the last 15 years showing that under certain circumstances ß-blockers are able to reduce the symptoms in some patients. Two large mortality trials had been performed with metoprolol and bisoprolol. Whereas, metoprolol, (MDC-trial, Waagstein et al.) examined in patients with dilated cardiomyopathy did not show reduction in mortality, the results of a study with bisoprolol (CIBIS trial) showed inconsistent results. Whereas the larger group of patients suffering from ischemic heart failure, had no benefit with respect to mortality, a small subgroup of patients with dilated cardiomyopathy had some positive effects.

Carvedilol was investigated in an earlier study in a few patients with CHF. The pilot trial was the investigation published by Das Gupta (document (1)).
In this small trial only hemodynamics and exercise capacity were evaluated. Bearing in mind, that there is no correlation between effects on hemodynamics / exercise capacity and effect on mortality, the next larger trials (US programme; the basis of the present patent application) did not give any idea for the expectation of positive results in mortality during the planning phase. This can be documented by the fact that the primary endpoint of this large US programme was exercise capacity, whereas mortality was not a pre-specified efficacy parameter. Mortality was only monitored by a drug safety monitoring board (DSMB), which was independent from the investigators and the sponsor of the study. This DSMB was installed in the study programme since a lot of previous studies with various investigational drugs have shown that improvement of symptoms and hemodynamics were

associated with increase (!) in mortality. Therefore, this board was installed to stop the study in case the risk of survival was inferior in comparison to the placebo-controlled patients. It should be noted that in the US programme all the patients received as basal medication the triple combination consisting of digitalis glycosides, diuretics and ACE-inhibitors. One group of the patients received then additionally carvedilol, the other group additionally only placebo. On the recommendations of the DSMB, the study programme was stopped prematurely due to ethical reasons because patients treated with placebo have shown a clear-cut higher mortality rate during the course of the study than the carvedilol treated patients. It should be noted that this effect must be regarded as additional to that obtained with ACE-inhibitors because all patients received ACE-inhibitors as basal medication.

Discussion of the cited prior art.

Document (1) = **J. Cardiovasc. pharmacol. 1992, 19 suppl. 1 PS62-7, Das Gupta p: et Al. "Can intravenous beta-blockade predict long-term hemodynamic benefit in chronic congestive heart failure secondary to ischemic heart disease? A comparison with oral carvedilol."** does not suggest in any way that carvedilol is a compound which is capable to reduce mortality resulting from heart failure (which is expressed in claim no. 1). Das Gupta's data only give some evidence for the improvement of haemodynamic variables or exercise capacity. It is well-known from extensive experience with various other investigational drugs (e.g.PDE-inhibitors) that improvement of haemodynamics of symptoms cannot be translated into expectation in mortality. It must be emphasized that over a long time it was the goal for the develop-

ment of new compounds designed for the treatment of heart failure to relieve the symptoms of the patients, since it was not possible to reduce mortality. Therefore, the experiences with carvedilol on mortality were unpredictable. First investigations with carvedilol (e.g. Das Gupta et al.) only show some positive effects on haemodynamics and symptoms.

It should be emphasized that therefore in the long-term studies in which the unexpected results on mortality were obtained and which are the basis for this application, the reduction of mortality was not prespecified endpoints of efficacy. Mortality was only a safety issue.

The dosing schedule demonstrated in Das Gupta paper is completely different from that what we have claimed in the present application.

Thus, there is no doubt that document (1) Das Gupta et al does not interfere with the present application.

Document (2) = J. Hypertens. Suppl, Jun 1993, 11 (4), Rosendorff C.: "Beta blocking agents with vasodilator activity.", see page S38, right hand column, line 15 -page S39, left-hand column, line 15, discloses that carvedilol has α_1-blocking activity (which has also been previously published several times). However, this property does not imply any expectation on improvement of life expectancy in patients with CHF. On the contrary, the V-HeFTI-study has shown that prazosin, the standard compound with α_1-antiadrenergic activities does not improve the mortality rate of patients with CHF.

Document (3) = Cardiology, 1993, 82 suppl. 3, P50-8,

Lessem JN et al: "Development of a multiaction beta-blocker." see in particular page 56, left-hand column, line 41 - right-hand column, line 20, discloses that carvedilol has been tested in patients with congestive heart disease. This article only announces that carvedilol is under clinical investigations in CHF. Again, this refers to Das Gupta (see no. 1) and no remarks on mortality are disclosed in this article.

Document (4) = Drug saf. August 1994, 11 (2), P86-93, Louis WJ et Al: "A risk benefit assessment of carvedilol in the treatment of cardiovascular disorders." see in particular page 90, left-hand column, line 29 - right hand column, line 2, reports that carvedilol has bee extensively studied in the management of heart failure. This paper gives information on running studies only. Two abstracts are cited which again give summaries of small studies having investigated haemodynamics but not mortality.

Document (5) = Drugs Feb 1993, 45 (2) Pages 232-58, Mctavish D et Al: "Carvedilol. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy." see in particular page 251, right-hand column, line 8 - page 252, left-hand column, line 12, discloses the activity of carvedilol in patients with congestive heart failure at doses of 12.5 to 50 mg twice daily and the use of carvedilol in combination with other drugs such as for instance hydrochlorothiazide.
In this paper the data from Das Gupta et al (see no. 1) are referred to (see above).

Document (6) = J. Cardiovasc. pharmacol. 1992, 19 suppl. 1 PS117-21, Senior R et Al. "Effects of carvedilol on ventricular arrhythmias." see the whole document especially the abstract lines 11-14, relates to the ben-

eficial effects of carvedilol on left ventricular function in a group of patients with congestive heart failure. This article exclusively deals with influence of carvedilol on arrhythmias in various cardiovascular disorders. The publication is a meta-analysis of some studies performed in this hospital. The patients with CHF mentioned in this paper, are the same patients described in the paper of Das Gupta (doc. (1)). In the abstract of this article it is mentioned that the improvement in premature ventricular contractions (PVC) may produce significant improvement in mortality. However, this statement is not elaborated in the paper any more. It must be emphasized that most of the patients with CHF die due to pump failure as outlined in the present application p. 1, line 26. Indeed, it can be assumed that the reduction in PVC does not provide a major contribution of reduction of mortality in patients with CHF. Thus, it has been shown in various investigations in the past that antiarrhythmic agents cannot reduce mortality. The most cited study is the CAST-study (Epstein et al. 1991) which has shown that the antiarrhythmic agents flacainide and encainide increase mortality. Also some investigational antiarrhythmic drugs were withdrawn from further development due to unfavourable results of mortality (e.g. Waldo et al. 1996). Thus, there is no evidence that antiarrhythmic activity per se provide potential for improving life expectancy. Also, the long-term trials with carvedilol on CHF which are the basis of this application, do not give evidence that reduction in PVC may dominantly be responsible for the reduction in mortality of patients treated with carvedilol. It should be noted that the ECG data of the Das Gupta study (see doc. 1) were available within the company long time before Senior's paper (no. 6) was published. Despite the knowledge of the data, the protocol of the CHF programme of carvedilol in US was mainly focused on exercise capacity as efficacy endpoint, but not

on mortality taking into account that a reduction in PVC's short-term studies does not provide a rationale for a long-term mortality study. Again, the results on mortality, found in the US study programme, were surprising and unpredictable and can therefore be regarded as an invention.

The present application satisfies the criterion set forth in Articles 33(2) and (3) PCT since the subject-matter of Claims 1 to 12 is new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT) and involves an inventive step (Rule 65(1)(2) PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4155/0A/WOWb		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP 96/ 00498	07/02/1996	08/02/1995
International Patent Classification (IPC) or national classification and IPC		
A61K31/40		
Applicant		
BOEHRINGER MANNHEIM PHARMACEUTICALS CORP. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consists of a total of 1 sheet.

3. This report contains indications and corresponding pages relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/07/1996	06.05.97
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	I. Obrecht Telephone No. 8471

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.
PCT/EP96/00498

I. Basis of the report

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[ ] the international application as originally filed.

[x] the description, pages 1 - 14, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____,

[x] the claims, Nos. 1 - 10, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 11, 12, filed with the letter of 17.03.97,
Nos. _____, filed with the letter of _____,

[ ] the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[ ] the description, pages _____.
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[ ] the drawings, sheets/fig _____.

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4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1 - 12	YES
	Claims	NO
Inventive Step (IS)	Claims 1 - 12	YES
	Claims	NO
Industrial Applicability (IA)	Claims 1 - 12	YES
	Claims	NO

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For the treatment of CHF, digitalis glycosides, (loop-) diuretics and vasodilators have been used over decades. Digitalis glycosides increase the myocardial

contractility, improve hemodynamic variables and improve symptoms, but digitalis glycosides do not increase life expectancy as confirmed recently in the large epidemiological DIG-trial on about 7800 patients. Diuretics offload the heart by reducing the circulating blood volume and therefore, symptoms, in particular congestions, can be reduced by diuretics. There is no study available which shows that diuretics are able to reduce the mortality of CHF patients. This topic has never been studied. Also vasodilators can reduce the myocardial pre- and afterload and therefore, they can improve the symptoms. Among the different vasodilators, there are inconsistent data available with respect to reduction in mortality. Whereas α_1-adrenoreceptor have not been shown to reduce mortality, the combination of hydralazine + isosorbid dinitrate have been shown to improve the life expectancy to a very small extend (Cohn et Al 1986). Phosphodiesterase inhibitors (e.g. milrinone) induce very nice hemodynamic effects and improve exercise capacity, but they induces excess mortality (Di Bianco et al. 1989).

On the other hand, in a variety of studies, ACE inhibitors have consistently demonstrated to be effective not only in improving the symptoms but also in a prolongation of life expectancy. In summary, there is no correlation between improvement of hemodynamic variables or relief of symptoms and reduction in mortality of patients treated with various drugs. Thus, the goal, to treat the patients for feeling better and living longer was an wish not met in the past due to the fact that life expectancy could mostly not be improved by the compounds.

With respect to ß-blockers:

In general, ß-blockers are contra-indicated for patients in CHF due to their negative inotropic effect. However, some studies have been performed in the last 15 years showing that under certain circumstances ß-blockers are able to reduce the symptoms in some patients. Two large mortality trials had been performed with metoprolol and bisoprolol. Whereas, metoprolol, (MDC-trial, Waagstein et al.) examined in patients with dilated cardiomyopathy did not show reduction in mortality, the results of a study with bisoprolol (CIBIS trial) showed inconsistent results. Whereas the larger group of patients suffering from ischemic heart failure, had no benefit with respect to mortality, a small subgroup of patients with dilated cardiomyopathy had some positive effects.

Carvedilol was investigated in an earlier study in a few patients with CHF. The pilot trial was the investigation published by Das Gupta (document (1)).
In this small trial only hemodynamics and exercise capacity were evaluated. Bearing in mind, that there is no correlation between effects on hemodynamics / exercise capacity and effect on mortality, the next larger trials (US programme; the basis of the present patent application) did not give any idea for the expectation of positive results in mortality during the planning phase. This can be documented by the fact that the primary endpoint of this large US programme was exercise capacity, whereas mortality was not a pre-specified efficacy parameter. Mortality was only monitored by a drug safety monitoring board (DSMB), which was independent from the investigators and the sponsor of the study. This DSMB was installed in the study programme since a lot of previous studies with various investigational drugs have shown that improvement of symptoms and hemodynamics were

associated with increase (!) in mortality. Therefore, this board was installed to stop the study in case the risk of survival was inferior in comparison to the placebo-controlled patients. It should be noted that in the US programme all the patients received as basal medication the triple combination consisting of digitalis glycosides, diuretics and ACE-inhibitors. One group of the patients received then additionally carvedilol, the other group additionally only placebo. On the recommendations of the DSMB, the study programme was stopped prematurely due to ethical reasons because patients treated with placebo have shown a clear-cut higher mortality rate during the course of the study than the carvedilol treated patients. It should be noted that this effect must be regarded as additional to that obtained with ACE-inhibitors because all patients received ACE-inhibitors as basal medication.

Discussion of the cited prior art.

Document (1) = **J. Cardiovasc. pharmacol. 1992, 19 suppl. 1 PS62-7, Das Gupta p: et Al. "Can intravenous beta-blockade predict long-term hemodynamic benefit in chronic congestive heart failure secondary to ischemic heart disease? A comparison with oral carvedilol."** does not suggest in any way that carvedilol is a compound which is capable to reduce mortality resulting from heart failure (which is expressed in claim no. 1). Das Gupta's data only give some evidence for the improvement of haemodynamic variables or exercise capacity. It is well-known from extensive experience with various other investigational drugs (e.g.PDE-inhibitors) that improvement of haemodynamics of symptoms cannot be translated into expectation in mortality. It must be emphasized that over a long time it was the goal for the develop-

ment of new compounds designed for the treatment of heart failure to relieve the symptoms of the patients, since it was not possible to reduce mortality. Therefore, the experiences with carvedilol on mortality were unpredictable. First investigations with carvedilol (e.g. Das Gupta et al.) only show some positive effects on haemodynamics and symptoms.

It should be emphasized that therefore in the long-term studies in which the unexpected results on mortality were obtained and which are the basis for this application, the reduction of mortality was not prespecified endpoints of efficacy. Mortality was only a safety issue.

The dosing schedule demonstrated in Das Gupta paper is completely different from that what we have claimed in the present application.

Thus, there is no doubt that document (1) Das Gupta et al does not interfere with the present application.

Document (2) = J. Hypertens. Suppl, Jun 1993, 11 (4), Rosendorff C.: "Beta blocking agents with vasodilator activity.", see page S38, right hand column, line 15 -page S39, left-hand column, line 15, discloses that carvedilol has α_1-blocking activity (which has also been previously published several times). However, this property does not imply any expectation on improvement of life expectancy in patients with CHF. On the contrary, the V-HeFTI-study has shown that prazosin, the standard compound with α_1-antiadrenergic activities does not improve the mortality rate of patients with CHF.

Document (3) = Cardiology, 1993, 82 suppl. 3, P50-8,

Lessem JN et al: "Development of a multiaction beta-blocker." see in particular page 56, left-hand column, line 41 - right-hand column, line 20, discloses that carvedilol has been tested in patients with congestive heart disease. This article only announces that carvedilol is under clinical investigations in CHF. Again, this refers to Das Gupta (see no. 1) and no remarks on mortality are disclosed in this article.

Document (4) = Drug saf. August 1994, 11 (2), P86-93, Louis WJ et Al: "A risk benefit assessment of carvedilol in the treatment of cardiovascular disorders." see in particular page 90, left-hand column, line 29 - right hand column, line 2, reports that carvedilol has bee extensively studied in the management of heart failure. This paper gives information on running studies only. Two abstracts are cited which again give summaries of small studies having investigated haemodynamics but not mortality.

Document (5) = Drugs Feb 1993, 45 (2) Pages 232-58, Mctavish D et Al: "Carvedilol. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy." see in particular page 251, right-hand column, line 8 - page 252, left-hand column, line 12, discloses the activity of carvedilol in patients with congestive heart failure at doses of 12.5 to 50 mg twice daily and the use of carvedilol in combination with other drugs such as for instance hydrochlorothiazide.
In this paper the data from Das Gupta et al (see no. 1) are referred to (see above).

Document (6) = J. Cardiovasc. pharmacol. 1992, 19 suppl. 1 PS117-21, Senior R et Al. "Effects of carvedilol on ventricular arrhythmias." see the whole document especially the abstract lines 11-14, relates to the ben-

eficial effects of carvedilol on left ventricular function in a group of patients with congestive heart failure. This article exclusively deals with influence of carvedilol on arrhythmias in various cardiovascular disorders. The publication is a meta-analysis of some studies performed in this hospital. The patients with CHF mentioned in this paper, are the same patients described in the paper of Das Gupta (doc. (1)). In the abstract of this article it is mentioned that the improvement in premature ventricular contractions (PVC) may produce significant improvement in mortality. However, this statement is not elaborated in the paper any more. It must be emphasized that most of the patients with CHF die due to pump failure as outlined in the present application p. 1, line 26. Indeed, it can be assumed that the reduction in PVC does not provide a major contribution of reduction of mortality in patients with CHF. Thus, it has been shown in various investigations in the past that antiarrhythmic agents cannot reduce mortality. The most cited study is the CAST-study (Epstein et al. 1991) which has shown that the antiarrhythmic agents flacainide and encainide increase mortality. Also some investigational antiarrhythmic drugs were withdrawn from further development due to unfavourable results of mortality (e.g. Waldo et al. 1996). Thus, there is no evidence that antiarrhythmic activity per se provide potential for improving life expectancy. Also, the long-term trials with carvedilol on CHF which are the basis of this application, do not give evidence that reduction in PVC may dominantly be responsible for the reduction in mortality of patients treated with carvedilol. It should be noted that the ECG data of the Das Gupta study (see doc. 1) were available within the company long time before Senior's paper (no. 6) was published. Despite the knowledge of the data, the protocol of the CHF programme of carvedilol in US was mainly focused on exercise capacity as efficacy endpoint, but not

on mortality taking into account that a reduction in PVC's short-term studies does not provide a rationale for a long-term mortality study. Again, the results on mortality, found in the US study programme, were surprising and unpredictable and can therefore be regarded as an invention.

The present application satisfies the criterion set forth in Articles 33(2) and (3) PCT since the subject-matter of Claims 1 to 12 is new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT) and involves an inventive step (Rule 65(1)(2) PCT).

11. The use of carvedilol according to claim 10, whereby carvedilol is administered in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of an angiotensin converting enzyme inhibitor, a diuretic and a cardiac glycoside.

12. Use of a compound according to claim 1 for the preparation of a medicament for the treatment of CHF to be administered in a daily maintenance dose of 10 - 100 mg, said medicament being administered in incremental dosage schems comprising three dose regimens, the first regimen comprising administering an amount of 10 - 30 % of the daily maintenance dose of the compound for a period of 7 - 28 days, the second regimen comprising administering an amount of 20 - 70 % of said daily dose for a period of 7 - 28 days and a third regimen comprising administering 100 % of said daily dose starting after termination of the second regimen.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/EP 96 / 00498
International Application No.

07 FEB 1996 (07. 02. 96)
International Filing Date

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference (if desired) (12 characters maximum): 4155/OA/WO-Wb

Box No. I TITLE OF INVENTION METHOD OF TREATMENT FOR DECREASING MORTALITY RESULTING FROM CONGESTIVE HEART FAILURE

Box No. II APPLICANT

Name and address: (*Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.*)

Boehringer Mannheim Pharmaceuticals Corporation
Smith Kline Beecham Corporation
Limited Partnership No. 1
101 Orchard Ridge Drive
Gaithersburg, MD 20878
United States

☐ This person is also inventor.

Telephone No.: 0621/759-2285
Facsimile No.: 0621/759-4457
Teleprinter No.:

State (*i.e. country*) of nationality: US

State (*i.e. country*) of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (*Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.*)

RO/EP

Mary Ann LUKAS-LASKEY
1019 Great Springs Road
Rosemont, PA 19010
US

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only (*If this check-box is marked, do not fill in below.*)

State (*i.e. country*) of nationality: US

State (*i.e. country*) of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: (*Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.*)

WEBER, Manfred
BOEHRINGER MANNHEIM GMBH
- Patent Department -
D-68298 Mannheim
Germany

Telephone No.: 0621/759-2285
Facsimile No.: 0621/759-4456
Teleprinter No.:

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

CONFIRMATION COPY

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)*

Robert RUFFOLO, Jr.
725 Pughtown Road
Spring City, PA 19475
US

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)*

Neil SHUSTERMAN
451 Ballytore Road
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US

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)*

Gisbert SPONER
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This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: DE

State *(i.e. country)* of residence: DE

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)*

Klaus STREIN
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DE

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: DE

State *(i.e. country)* of residence: DE

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [X] **AP** **ARIPO Patent:** **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] **EA** **Eurasian Patent:** **AZ** Azerbaijan, **BY** Belarus, **KZ** Kazakstan, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **DE** Germany, **DK** Denmark, **ES** Spain, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [X] **AL** Albania
- [X] **AM** Armenia .....
- [X] **AT** Austria .....
- [X] **AU** Australia .....
- [X] **AZ** Azerbaijan
- [X] **BB** Barbados
- [X] **BG** Bulgaria .....
- [X] **BR** Brazil .....
- [X] **BY** Belarus
- [X] **CA** Canada
- [X] **CH and LI** Switzerland and Liechtenstein
- [X] **CN** China .....
- [X] **CZ** Czech Republic .....
- [X] **DE** Germany .....
- [X] **DK** Denmark .....
- [X] **EE** Estonia .....
- [X] **ES** Spain .....
- [X] **FI** Finland .....
- [X] **GB** United Kingdom
- [X] **GE** Georgia .....
- [X] **HU** Hungary .....
- [X] **IS** Iceland
- [X] **JP** Japan .....
- [X] **KE** Kenya .....
- [X] **KG** Kyrgyzstan .....
- [X] **KP** Democratic People's Republic of Korea .....
- [X] **KR** Republic of Korea .....
- [X] **KZ** Kazakstan .....
- [X] **LK** Sri Lanka
- [X] **LR** Liberia
- [X] **LS** Lesotho .....
- [X] **LT** Lithuania
- [X] **LU** Luxembourg .....
- [X] **LV** Latvia
- [X] **MD** Republic of Moldova .....
- [X] **MG** Madagascar .....
- [X] **MK** The former Yugoslav Republic of Macedonia .....
- [X] **MN** Mongolia
- [X] **MW** Malawi .....
- [X] **MX** Mexico .....
- [X] **NO** Norway
- [X] **NZ** New Zealand .....
- [X] **PL** Poland .....
- [X] **PT** Portugal .....
- [X] **RO** Romania
- [X] **RU** Russian Federation .....
- [X] **SD** Sudan
- [X] **SE** Sweden
- [X] **SG** Singapore
- [X] **SI** Slovenia .....
- [X] **SK** Slovakia .....
- [X] **TJ** Tajikistan .....
- [X] **TM** Turkmenistan .....
- [X] **TR** Turkey .....
- [X] **TT** Trinidad and Tobago .....
- [X] **UA** Ukraine .....
- [X] **UG** Uganda .....
- [X] **US** United States of America .....
- [X] **UZ** Uzbekistan .....
- [X] **VN** Viet Nam .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- [ ] .....
- [ ] .....
- [ ] .....
- [ ] .....

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of _____.

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) Deutschland	08. Februar 1995 (08.02.1995)	195 03 995.5	
item (2) U S	07. Juni 1995 (07.06.1995)	08/483,635	
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☐ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) : _____

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA /_____

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request.*

Country (or regional Office): Date *(day/month/year)*: Number:

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	4	sheets
2. description	14	sheets
3. claims	4	sheets
4. abstract	2	sheets
5. drawings		sheets
Total	24	sheets

This international application is accompanied by the item(s) marked below:

1. ☒ separate signed power of attorney ~~1 following~~
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☐ priority document(s) *identified in Box No. VI as item(s):* 1 following
5. ☒ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. ☒ other *(specify)*: stamped addressed envelope

Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

M. Weber

Dr. Manfred Weber
European Patent Attorney

For receiving Office use only

1. Date of actual receipt of the purported international application: 07 FEB 1996 (07. 02. 96)
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

CONFIRMATION COPY

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
BOEHRINGER MANNHEIM GMBH
Patentabteilung
Attn. Weber, Manfred
D-68298 Mannheim
GERMANY

Applicant's or agent's file reference 4155/OA/WOWb	Date of mailing *(day/month/year)* 21/08/96
International application No. PCT/EP 96/00498	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant BOEHRINGER MANNHEIM PHARMACEUTICALS CORP. et al.	International filing date *(day/month/year)* 07/02/96

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? To the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2; the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicants's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Monika Schmitz

Form PCT/ISA/220 (July 1992)

T 21.10.96 WOWb

NOTES TO FORM PCT/ISA/220

These notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments wil be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

NOTES TO FORM PCT/ISA/220 (continued)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; Claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 TO 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings which cannot be amended under Article 19(1).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confouded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

In what language?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English of French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
4155/OA/WOWb		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 96/00498	07/02/96	08/02/95

Applicant

BOEHRINGER MANNHEIM PHARMACEUTICALS CORP. et al.

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

   [ ] filed with the international application.

   [ ] furnished by the applicant separately from the international application,

      [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

   [ ] Transcribed by this Authority

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   USE OF CARBAZOLE COMPOUNDS FOR THE TREATMENT OF CONGESTIVE HEART FAILURE

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 96/00498

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,2,7-9,12
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please see annex

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

The expression "a compound which is both a beta-adrenoreceptor antagonist and an alpha 1-adrenoreceptor antagonist" is not a clear and concise definition of a chemical compound because it is not known which compounds would (and would not) fulfil these requirements. Because of the use of this open-ended expression a comprehensive search would involve a major part of the chemistry related IPC classes. Such a search is economically not feasible. The search has therefore had to be restricted to the specifically claimed compounds.
Furthermore, due to the large number of compounds which are theoretically defined by the formula of claim 2 the search had to be further restricted on economic grounds to the preferred compound and the general concept of the application.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/00498

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	PREVENTION AND MANAGEMENT OF CONGESTIVE HEART FAILURE, 1996, 2/1 (39-40), USA, XP000578645 TEPPER D.: "Multicenter oral carvedilol heart failure assessment (MOCHA): A six-month dose-response evaluation in class II-IV patients: Comment" see the whole document ---	1-14
P,X	CIRCULATION, JUL 15 1995, 92 (2) P212-8, UNITED STATES, XP000578584 "Effects of carvedilol, a vasodilator-beta-blocker, in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group." see the whole document --- -/--	1-14

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 1996	21.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Mair, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J CARDIOVASC PHARMACOL, 1992, 19 SUPPL 1 PS62-7, UNITED STATES, XP000578581 DASGUPTA P ET AL: "Can intravenous beta-blockade predict long-term hemodynamic benefit in chronic congestive heart failure secondary to ischemic heart disease? A comparison of intravenous with oral carvedilol." see the whole document	1-14
X	J HYPERTENS SUPPL, JUN 1993, 11 (4) PS37-40, ENGLAND, XP000578568 ROSENDORFF C: "Beta-blocking agents with vasodilator activity." see page S38, right-hand column, line 15 - page S39, left-hand column, line 15	1-14
X	CARDIOLOGY, 1993, 82 SUPPL 3 P50-8, SWITZERLAND, XP000578573 LESSEM JN ET AL: "Development of a multiaction beta blocker. Scientific challenges and regulatory needs." see page 56, left-hand column, line 41 - right-hand column, line 20	1-14
X	DRUG SAF, AUG 1994, 11 (2) P86-93, NEW ZEALAND, XP000578570 LOUIS WJ ET AL: "A risk-benefit assessment of carvedilol in the treatment of cardiovascular disorders." see page 90, left-hand column, line 29 - right-hand column, line 2	1-14
X	DRUGS, FEB 1993, 45 (2) P232-58, NEW ZEALAND, XP000578564 MCTAVISH D ET AL: "Carvedilol. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy." see page 251, right-hand column, line 8 - page 252, left-hand column, line 12	1-14
X	J CARDIOVASC PHARMACOL, 1992, 19 SUPPL 1 PS117-21, UNITED STATES, XP000578580 SENIOR R ET AL: "Effects of carvedilol on ventricular arrhythmias." see the whole document especially abstract line 11-14	1-14

1

PATENT COOPERATION TREATY

PCT

08/875603

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
4155/OA/WOWb		
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/EP 96/00498	07/02/96	08/02/95
Applicant		
BOEHRINGER MANNHEIM PHARMACEUTICALS CORP. et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant.
   - [X] the text has been established by this Authority to read as follows:

   USE OF CARBAZOLE COMPOUNDS FOR THE TREATMENT OF CONGESTIVE HEART FAILURE

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 96/00498

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,2,7-9,12
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please see annex

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

The expression "a compound which is both a beta-adrenoreceptor antagonist and an alpha 1-adrenoreceptor antagonist" is not a clear and concise definition of a chemical compound because it is not known which compounds would (and would not) fulfil these requirements. Because of the use of this open-ended expression a comprehensive search would involve a major part of the chemistry related IPC classes. Such a search is economically not feasible. The search has therefore had to be restricted to the specifically claimed compounds.
Furthermore, due to the large number of compounds which are theoretically defined by the formula of claim 2 the search had to be further restricted on economic grounds to the preferred compound and the general concept of the application.

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

To:
Weber, Manfred
BOEHRINGER MANNHEIM GmbH
Patentabteilung
Sandhofer Str. 116
D-68298 MANNHEIM
ALLEMAGNE

Date of mailing (day/month/year) 12 MAR 1996

Applicant's or agent's file reference
4155/OA/WOWb

IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP 96/00498	07/02/1996	08/02/1995

Applicant
BOEHRINGER MANNHEIM PHARMACEUTICALS CORPORATION

Title of the invention

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.
2. The applicant is further notified that the record copy of the international application was transmitted to the International Bureau on the above date of mailing.
3. ☐ Other:

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

Name and mailing address of the receiving Office
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Y. Martinus-v.d. Nouwelant

Form PCT/RO/105 (0792) P20402

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

COMMUNICATION OF
INTERNATIONAL APPLICATIONS

(PCT Article 20)

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as designated Office

Date of mailing:
03 October 1996 (03.10.96)

The International Bureau transmits herewith copies of the international applications having the following international application numbers and international publication numbers:

International application no.:	International publication no.:
PCT/EP96/00498	WO96/24348

CORRECTED VERSION
VERSION CORRIGEE

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 730.91.11

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 4155/OA/WO-Wb

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/EP96/00498	07. Februar 1996 (07.02.1996)	08. Februar 1995 (08.02.1995)

Title of invention: METHOD OF TREATMENT FOR DECREASING MORTALITY RESULTING FROM CONGESTIVE HEART FAILURE

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Boehringer Mannheim Pharmaceuticals Corporation
Smith Kline Beecham Corporation
Limited Partnership No. 1
101 Orchard Ridge Drive
Gaithersburg, MD 20878
United States

Telephone No.: 0621/759-2285
Facsimile No.: 0621/759-4457
Teleprinter No.:

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LUKAS-LASKEY, Mary Ann
1019 Great Springs Road
Rosemont, PA 19010
US

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RUFFOLO, Jr., Robert
725 Pughtown Road
Spring City, PA 19475
US

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
US	US

[X] Further applicants are indicated on a continuation sheet.

Sheet No. .2.

International application No.

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet is not to be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SHUSTERMAN, Neil
451 Ballytore Road
Wynnewood, PA 19096
US

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SPONER, Gisbert
Lessingstr. 13
D-69514 Laudenbach
DE

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
DE	DE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

STREIN, Klaus
Eichenstr. 45
D-69503 Hemsbach
DE

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
DE	DE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

International application No.

Box No. III AGENT OR COMMON REPRESENTATIVE: OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WEBER, Manfred
c/o BOEHRINGER MANNHEIM GMBH
- Patent Deaprtment -
D-68298 Mannheim
DE

Telephone No.: 0621/759-2285

Facsimile No.: 0621/759-4457

Teleprinter No.:

[ ] Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the International Preliminary Examining Authority*

(i) [X] to start the international preliminary examination on the basis of the international application as originally filed.

(ii) [ ] to take into account the amendments under Article 34 of

- [ ] the description (amendments attached).
- [ ] the claims (amendments attached).
- [ ] the drawings (amendments attached).

(iii) [ ] to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).

(iv) [ ] to disregard any amendments of the claims made under Article 19 and to consider them as reversed.

(v) [ ] to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Box No. V ELECTION OF STATES

[X] The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)* except .....

(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)

Sheet No. 4.

International application No.

Box No. VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only: received	not received
1. amendments under Article 34				
description	:	sheets	☐	☐
claims	:	sheets	☐	☐
drawings	:	sheets	☐	☐
2. letter accompanying amendments under Article 34	:	sheets	☐	☐
3. copy of amendments under Article 19	:	sheets	☐	☐
4. copy of statement under Article 19	:	sheets	☐	☐
5. other *(specify)*:	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☒ fee calculation sheet
5. ☒ other *(specify)*: stamped addressed envelope

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

M. Weber

Dr. Manfred Weber
European Patent Attorney

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/EP96/00498	For International Preliminary Examining Authority use only
Applicant's or agent's file reference 41550AWO	Date stamp of the IPEA
Applicant Boehringer Mannheim Pharmaceuticals Corporation Smith Kline Beecham Corporation	

Calculation of prescribed fees

1. Preliminary examination fee	DM 3 000,--	P	
2. Handling fee	DM 292,--	H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	DM 3 292,-- TOTAL		

Mode of Payment

[X]	authorization to charge deposit account with the IPEA (see below)	[ ]	cash
[ ]	cheque	[ ]	revenue stamps
[ ]	postal money order	[ ]	coupons
[ ]	bank draft	[ ]	other *(specify)*:

Deposit Account Authorization *(this mode of payment may not be available at all IPEAs)*

The IPEA/ Mii [X] is hereby authorized to charge the total fees indicated above to my deposit account.

[X] *(this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

BOEHRINGER MANNHEIM GMBH
ppa. i.V.

2800 0020	July 16, 1996 /Ha	Dr. Fouquet	Dr. Weber
Deposit Account Number	Date *(day/month/year)*	Signature	

See Notes to the fee calculation sheet